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EXAMINER	
SHARAREH, SHAHNAM J	

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/821,352	LASSER, ELLIOTT C.	
	Examiner	Art Unit	
	Shahnam Sharareh	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/7/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows:

Various types of X- Ray Contrast Media.

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

The claims are deemed to correspond to the species listed above in the following manner: 1-21.

The following claim(s) are generic: 1, 15, 18, 20.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: X-Ray contrast media include various types of ionic or nonionic moieties that do not share similar molecular, pharmacological or immunological characteristics. Therefore, they are viewed to lack a special corresponding technical feature.

During a telephone conversation with Marc Morley on November 18 a provisional election was made with traverse to prosecute the invention directed to species that read on iodinated contrast agents such as IOTROLAN, claims 1-21. Affirmation of this election must be made by applicant in replying to this Office action. Accordingly,

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating or propholactically treating allergic conjunctivitis or allergic rhinitis, does not reasonably provide enablement for treating or preventing all types of allergic reactions including drug allergies, food allergies, etc. Further, the specification does not adequately enable for methods of preventing allergic reactions in any susceptible subjects. Nor does it provide adequate enablement for using any type of X-Ray contrast media that could provide the intended benefits. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the

predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention provides for methods of treating or preventing all types of allergic reactions encompassing seasonal allergies as well as drug or food allergies comprising administering to a mammal an effective amount of any X-ray contrast media.

(2) The state of the prior art

Treating allergic reaction typically encompass methods of administering to a patient such agents as corticosteroids, antihistamines or mast cell stabilizers. Prior art does not provide any guidance as to specific utility of X-ray contrast agents as an anti-allergic medication.

(3) The relative skill of those in the art

The relative skill of the those in the art is high and includes all persons in the field of therapeutic or investigational medicine.

(4) The predictability or unpredictability of the art

The unpredictability of the field of therapeutic or investigational medicine is very high. The true facts on the state of the art relating to allergic reactions is expressed succinctly in the Frick's teachings in Basic & Clinical Immunology 2nd edition, IDS item #3, filed on September 07, 2004. The significance of such reactions is in the sequence of events leading to the release of pro-inflammatory mediators.

(5) The breadth of the claims

The claims are very broad. The claims read on treating or preventing any allergic type reaction with any X-ray contrast media.

(6) The amount of direction or guidance presented

The specification only teaches methods of treating or potentially propholactically treating seasonal allergic rhinitis or conjunctivitis with dimer-type iodinated contrast agents such as Iodixanol. There is no teaching directed to treating all allergic type reactions such as food or drug allergies. There is no teachings with respect to dosing, structural relationship or functional characteristics of the entire class of X-ray contrast media that treat allergic reactions. Neither is there any showing that the intended

therapeutic benefit is a function of a molecular similarity among all types of X-ray agents. In fact X-ray contrast media such as Iodinated benzene moieties for long have been associated with inducing allergenic reactions. See Carr et al, BR.J. Radiology, IDS item #2, filed on September 07, 2004.

Further, the specification provides no guidance as to how the allergic is prevented in susceptible subjects. The claims appear to be directed to methods of preventing the claimed pathological condition. There are not teachings as how subjects are deemed to be susceptible to any drug or food allergy or even potentially suffer from seasonal allergy. Moreover, the specification must provide direct evidence associating the claimed prevention to the contrast media applied. In this case, there is no teachings for screening methods identifying susceptible subjects nor is there any direct evidence of efficacy establishing a preventative property associated with the X-ray contrast media.

Since the state of the prior art concerning methods of preventing allergic reactions is not well described, nor does it provide for any absolute prevention, undue experimentation is necessary to determine screening and testing protocols to demonstrate the efficacy of the presently claimed invention.

(7) The presence or absence of working examples

As stated above, the specification discloses specific X-ray contrast media for specific type of allergic reactions.

(8) The quantity of experimentation necessary

Since the use of the entire scope of X-ray contrast media for treatment or prevention of all type of allergic reaction cannot be predicted, in view of the above-discussed factors, undue experimentation is needed for one of ordinary skill in the art to practice the entire scope of the instant claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 8-17 are rejected under 35 U.S.C. 102(b) as being anticipated Katayama et al. Radiology 1990; 175:621-628 (item #6, IDS filed on September 07, 2004).

Katayama describes a clinical study assessing the adverse reaction of patients who had received intravenous ionic or nonionic X-ray contrast media. Such contrast media included iopamidol, Iohexol or Ioxaglate which all fall within the scope of the instant claims (see abstract, page 621 at 2nd and 4th para). Katayam describes that patients where identified based on the history of their allergy (see page 621 at 5th para under patient data). In fact, Katayam describes administration of ionic or non ionic X-ray contrast agents to such patients with history of Allergy (see page 625 under the heading ADRs by History of Allergy). The doses used in Katayama falls within the scope of the instantly claimed effective amounts because the instant claims embrace such doses up to 100 grams of the contrast media (see Katayama at page 627 under ADRs by Dose, Also see instant specification at para 0012 to ascertain the metes and bounds of the instantly claimed amount of an X-ray contrast media). Accordingly, Katayama teaches all elements and method steps of the instant claims.

In a claim drawn to a process, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963). Since Katayama teaches all elements and method steps of the instant claims, his methods would inherently anticipate the functional limitations of the instant claims including the blocking of antigen-antibody complex formation or reducing an allergic reaction.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 7-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lasser et al (Acad Radiol 1998;5 (Suppl 1):S95-S98, item #13, IDS filed on Sept 07, 2004) in view of Roitt et al, Mosby Co, Ltd, 1985, pages 19.1, 19.7-19.10).

Lasser et al studied the effects of dimeric ionic and nonionic X-ray contrast agents such as iotrolan, ioversol, ioxalate, and iopamidol in vitro and in vivo in rats (abstract, see page S96 2nd-4th para). The employed X-ray contrast agents are dimeric or ionic molecues that can bind to immunoglobulins such as IgM or IgG. (see abstract). Lasser injects such amounts, which falls within the limitations of the instant claims (see S94 2nd para and S96, 2nd para). Lasser concluded that such contrast media can compete with the binding of different antigens to their respective IgG antibodies. (see S96 3rd and 7th para.). Lasser states that such contrast media can function as nonspecific pseudoantigens and will aggregate on the surface of mast cells or basophils or act as immune complexes to block formation of antigen-immunoglobulin complex. (see page S97 the entire page). Accordingly, Lasser concludes that contrast agents can

cause antigen excess and lead to inhibition of cellular content, which mediates histamine release (S97 at 2nd col-S98 1st para). Lasser merely fail to explicitly show administration a contrast agent for treatment of an allergic reaction.

Roitt et al is merely used to show that allergic and hypersensitivity reactions are mediated by mast cell activation through antibody complex formation and the release of proinflammatory mediators (see 19.1 type 1, and 19.7-19.10).

Thus, it would have been obvious to one of ordinary skill in the art at the time of invention to administer such agents as described by Lasser to a mammal for purposes of treating an allergic reaction by inhibiting mast cell activation, because as described by Roitt, the allergic reaction is mediated by mast cell activation at their cell surface.

The ordinary skill in the art would have had a reasonable expectation of success, because as described by Lasser, contrast agents are expected to aggregate at the surface of mast cells or basophils and interfere with the binding of antibodies at mast cell surface.

Claims 2-6 and 18-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lasser et al in view of Roitt as applied to claims 1, 7-17 and further in view of Bhargava et al. (Drugs of Today, 1998; 34(11), 957-971) and MacLeod et al (Clin Exp Allergy, 1997;27:1328-1334).

The teachings of Lasser and Roitt are described above. Their combined teachings fail to explicitly describe the topical administration of contrast agents for treatment of allergic conjunctivitis or rhinitis.

Bhargava is merely used to show that topical mast cell stabilizers are readily used for treatment of allergic conjunctivitis and symptoms associated with seasonal rhinitis. (see abstract, pages 965-970).

MacLeod is used to show that conjunctival mast cells contain various types of proinflammatory mediators and that inhibition of mast cells can reduce the allergic response in allergic conjunctivitis. (See pages 1333-1334).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to further administer a contrast agent such as iotrolan to a mammal via topical routes, because as suggested by Bhargava, topical administration of mast cell stabilizers has been proven effective against the symptoms of allergic conjunctivitis or rhinitis.

Furthermore, as taught by MacLeod, conjunctiva mast cells contain various types of proinflammatory mediators; therefore, one of ordinary skill in the art would have had reasonable expectation of success in stabilizing such mast cells when locally administering contrast media of Lasser to conjunctiva.

Conclusion

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh whose telephone number is 571-272-0630. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, PhD can be reached on 571-272-0629. The

fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SHENGJUN WANG
PRIMARY EXAMINER

S. Wang